REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(06-12-2016)*	**2. REPORT TYPE**	**3. DATES COVERED** *(From - To)*
	FINAL	July 2009-June 2011

4. TITLE AND SUBTITLE

Pharmacokinetics of IM,IV and IO Atropine in Normovolemic and Hypovolemic Swine

5a. CONTRACT NUMBER
N/A

5b. GRANT NUMBER
HU0001-09-1-TS09

5c. PROGRAM ELEMENT NUMBER
N/A

6. AUTHOR(S)

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5d. PROJECT NUMBER
N09-P11

5e. TASK NUMBER
N/A

5f. WORK UNIT NUMBER
N/A

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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San Antonio, TX, 78234

8. PERFORMING ORGANIZATION REPORT NUMBER
N/A

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
TriService Nursing Research
Program, 4301 Jones Bridge RD
Bethesda, MD 20814

10. SPONSOR/MONITOR'S ACRONYM(S)
TSNRP

11. SPONSOR/MONITOR'S REPORT NUMBER(S)
N09-P11

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for public release; distribution unlimited

13. SUPPLEMENTARY NOTES
N/A

14. ABSTRACT

Purpose:
This study compared the pharmacokinetics of IV, IO, and IM atropine in cardiovascular collapse to determine the extent to which hypovolemic shock retards IM atropine absorption and if IO administration is an effective alternative.

Design:
This study was a prospective, between subjects, experimental design.

Methods:
Swine, under general anesthesia, were randomly assigned to one of six treatment groups: normovolemic IV, IO and IM and hypovolemic IV, IO and IM. Hypovolemia was accomplished by exsanguinating 35% of the estimated blood volume (24.5 ml/kg) over 30 minutes. 2 mg of atropine was delivered via IV, IO or IM injection and blood samples were collected over 2 hours. The samples were analyzed by HPLC-MS.

Sample:
Thirty-six Yorkshire-cross swine weighing between 58 and 71 Kilograms.

Analysis:
Pharmacokinetic parameters were determined using compartmental models. A multivariate analysis of variance was used to determine differences in the in the groups relative to the pharmacokinetic parameters with a post-hoc least significant difference test.

Findings:
Both IV and IO peaked immediately and had a very rapid distribution phase. As expected, the peak concentration and time to peak concentration were significantly lower for IM administration. The hypovolemic IO and IV groups had very similar results to the normovolemic groups, peaking immediately and having a rapid distribution. Compared to the normovolemic groups, peak concentrations were higher in the IO and IV hypovolemic groups and concentrations remained higher for the duration of the experiment. Hypovolemia significantly delayed the absorption after IM administration (6.6 vs 19.5 minutes, p=0.011).

Implications for Military Nursing:
This study emphasizes the potential difficulty of treating nerve agent poisoning solely with IM atropine and the feasibility of treating nerve agent casualties with IO administration of atropine. The IO route of administration may be particularly advantageous when the casualty has had a severe exposure or is in hypovolemic shock.

15. SUBJECT TERMS
Pharmacokinetics, cardiovascular collapse, Swine, Normovolemic, Hypovolemic

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
					Jaya Pothen
a. REPORT	b. ABSTRACT	c. THIS PAGE	UU	17	19b. TELEPHONE NUMBER *(include area code)*
UNCLASSIFIED	UNCLASSIFIED	UNCLASSIFIED			301-319-0596

TriService Nursing Research Program Final Report Cover Page

Sponsoring Institution	TriService Nursing Research Program
Address of Sponsoring Institution	4301 Jones Bridge Road Bethesda MD 20814
USU Grant Number	HU0001-09-1-TS09
USU Project Number	N09-P11
Title of Research Study or Evidence-Based Practice (EBP) Project	Pharmacokinetics of IM,IV and IO Atropine in Normovolemic and Hypovolemic Swine
Period of Award	1 July 2009 – 30 June 2011
Applicant Organization	The Geneva Foundation
Address of Applicant Organization	917 Pacific Avenue, Suite 600 Tacoma, WA 98402

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Mentor Signature Date 7 Oct 16

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Abstract

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TSNRP Research Priorities that Study or Project Addresses

Primary Priority

Force Health Protection:	☐ Fit and ready force ☒ Deploy with and care for the warrior ☐ Care for all entrusted to our care
Nursing Competencies and Practice:	☐ Patient outcomes ☐ Quality and safety ☐ Translate research into practice/evidence-based practice ☐ Clinical excellence ☐ Knowledge management ☐ Education and training
Leadership, Ethics, and Mentoring:	☐ Health policy ☐ Recruitment and retention ☐ Preparing tomorrow's leaders ☐ Care of the caregiver
Other:	☐

Secondary Priority

Force Health Protection:	☐ Fit and ready force ☐ Deploy with and care for the warrior ☐ Care for all entrusted to our care
Nursing Competencies and Practice:	☐ Patient outcomes ☐ Quality and safety ☐ Translate research into practice/evidence-based practice ☐ Clinical excellence ☐ Knowledge management ☐ Education and training
Leadership, Ethics, and Mentoring:	☐ Health policy ☐ Recruitment and retention ☐ Preparing tomorrow's leaders ☐ Care of the caregiver
Other:	☒ Evidence based

Progress Towards Achievement of Specific Aims of the Study or Project

Findings related to each specific aim, research or study questions, and/or hypothesis:

The aims of this study are as follows:

1. Determine the pharmacokinetics of atropine when administered via the IO, IV, and IM routes in a normovolemic pig model
2. Determine the pharmacokinetics of atropine when administered via the IO, IV, and IM routes in a hypovolemic pig model
3. Determine if there is a difference in the pharmacokinetics (particularly, a change in the rate and extent of absorption) of atropine when administered via the IO, IV, and IM routes in a normovolemic compared to a hypovolemic pig model?

Raw plasma concentration versus time curves for all groups are presented in Figure 1. Both IV and IO peaked immediately and had a very rapid distribution phase. There was no apparent absorption phase for the IO administration. As expected, the peak concentration and time to peak concentration were significantly lower for IM administration. The hypovolemic IO and IV groups had very similar results to the normovolemic groups, peaking immediately and having a rapid distribution. Compared to the normovolemic groups, peak concentrations were higher in the IO and IV hypovolemic groups and concentrations remained higher for the duration of the experiment (Figure 1). Hypovolemia did not delay the circulation or create an absorption phase in the IO administration. However, hypovolemia significantly delayed the absorption after IM administration (6.6 vs 19.5 minutes, $p=0.011$).

Both normovolemic and hypovolemic IV data were modeled using a 2 compartment model with IV bolus and first order elimination. No appreciable absorption phase was noted in the IO data; therefore, it was modeled using the same model as the IV data. The normovolemic IM data were modeled using a 2 compartment model, first order absorption and elimination. The hypovolemic IM data had such slow absorption that no distribution was observed in the concentration time curve and could not be modeled using the same model as the IM normovolemic data. Therefore, a 1 compartment model was used for modeling. The pharmacokinetic parameters derived from compartmental modeling are reported in Table 2. The peak concentration or concentration maximum (Cmax) and time to peak concentration (Tmax) for the IM hypovolemic group were significantly lower than hypovolemic IV and IO administration, as well as, significantly lower than all the normovolemic groups.

Figure 1. Pharmacokinetic profiles of atropine by route of administration

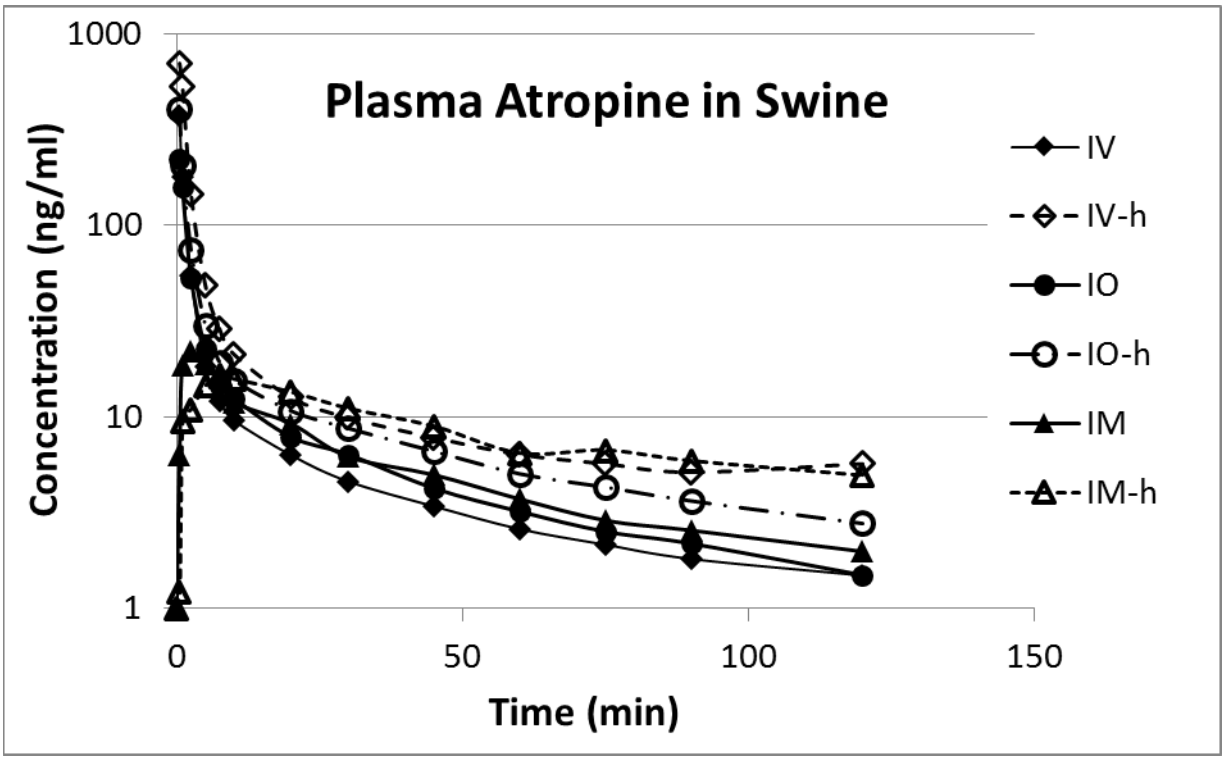

Table 1. Derived pharmacokinetic parameters of atropine in normovolemic and hypovolemic swine. Mean ± SD

		Normovolemic			Hypovolemic		
Parameters	Units	IV	IO	IM	IV	IO	IM
V1	L	6.5± 3.3	11.1± 7.2	65.2± 44.3	4.4± 1.6	7.7± 3.1	
Vss	L	71.5± 29.1	76.2± 36.0		46.6± 14.4	71.5± 35.4	
AUC	min*ng/ml	912± 334	1023± 384	937± 183	1599± 392	1470± 523	1247± 168
Cl	ml/min	2523± 1105	2184± 756	2200± 408	1314± 329	1462± 345	1627± 217
t½- alpha	min	0.9± 0.2	1.3± 0.4	7.3± 6.1	1.1± 0.1	1.2± 0.2	
t½- beta	min	38.3± 4.6	38.0± 6.9	106.0± 86.2	46.2± 5.3	48.9± 14.8	
Cmax	ng/ml	374± 166	300± 250	20± 8	513± 221	309± 168	14± 5
Tmax	min	0	0	6.6± 3.1	0	0	19.5± 9.8

The initial volume of distribution (V1), volume of distribution at steady state (Vss), area under the curve (AUC), clearance (Cl), and half-lives (t½- alpha, t½- beta) are descriptive in nature. Comparisons were made between the maximum concentration (Cmax) and time to maximum

concentration (Tmax) which describe the absorption of atropine from the site of injection to the blood stream.

Relationship of current findings to previous findings:

Our results support the bioequivalence of intraosseous and intravenous administration of atropine. In theory, drug could distribute to the bone marrow of the tibia, which is primarily fat, and slowly absorb over time. We did not see any evidence of this in our study.

Hypovolemia affected the pharmacokinetics of both intravenous and intraosseous administration. However, they did not affect one route to any greater degree. We hypothesized that hypovolemia may slow the onset of IO administration, creating an absorption phase. We did not see any evidence of an absorption phase. The pharmacokinetic changes we saw with hypovolemia after IO and IV administration were predictable. A 35% reduction in blood volume would cause a decrease in the initial volume of distribution and diminished liver blood flow generally causes a decrease in drug clearance. Our results are consistent with a small number of investigators that have used traditional compartmental modeling to elucidate the effects of hemorrhage on pharmacokinetics.[7,8] A study investigating the effects of hemorrhagic shock on the pharmacokinetics of fentanyl demonstrated higher peak concentrations, smaller volume of distribution, and decreased clearance.[7] Johnson and colleagues observed similar changes in an investigation determining the influence of hemorrhage on the pharmacokinetics of propofol.[8] We observed these same general changes with hypovolemia.

Effect of problems or obstacles on the results:

Thirty-six pigs were used in the study; one of which was excluded from data analysis. Specifically, one pig in the hypovolemic IV administration group died in the final minutes of the experiment. The data from that pig were analyzed and modelled but the results were vastly different (greater than three standard deviations) from the rest of the group and, therefore, excluded from statistical analysis.

Limitations:

The results may not be generalizable to humans; however, pigs are very similar in anatomy and physiology and should approximate results with humans. In fact, the tibia of a 70-kilogram pig is shorter and may contain less marrow than a human of the same weight. This difference may underestimate any distribution or depot effect. Additionally, the results may be specific to tibial IO administration and not generalizable to sternal IO administration. The sternum has a smaller marrow volume and is made up of red marrow compared to the adult tibia which is made up of almost entirely yellow marrow. In theory, the sternal IO route should exhibit less distribution because of its lower fat content and marrow volume. Additional studies should be conducted using the sternal IO route to elucidate potential differences.

Intramuscular auto-injection of atropine into the gluteal muscle of the pig produced similar pharmacokinetics to human IM administration with the MARK 1 auto-injector. Mean peak plasma concentrations in swine were 20 ng/ml compared to 12.9 ng/ml in the human. Mean time

to peak concentration (6.6 minutes) in the swine was almost identical to results in a human volunteer study (6.5 minute).[6]

It was not practical to blind investigators to experimental group. However, the outcomes were objective and unlikely affected by observer bias.

Conclusion:

The aims of this study were to determine the pharmacokinetics of atropine when administered via the IO, IV, and IM routes in a hypovolemic swine model and determine the impact of hypovolemia on the rate and extent of absorption when administered via these routes. This study demonstrated that hypovolemia had a dramatic effect on the absorption of atropine delivered by intramuscular auto-injection. We expected absorption from IM injection to decrease with the peripheral vasoconstriction associated with hypovolemia, but the three-fold increase in Tmax was more than we anticipated. Conversely, hypovolemia had less effect on IV and IO delivery. We hypothesized that peripheral vasoconstriction caused by hypovolemia might delay uptake from IO administration and create an absorption phase in its pharmacokinetic profile. In theory, drug could distribute to the bone marrow of the tibia, which is primarily fat, and slowly absorb over time. We did not see any evidence of this in our study.

This study emphasizes the potential difficulty of treating nerve agent poisoning solely with IM atropine and the feasibility of treating nerve agent casualties with IO administration of atropine. This route of administration may be particularly advantageous when the casualty has had a severe exposure or is in hypovolemic shock.

Significance of Study or Project Results to Military Nursing

The American Association of Colleges of Nursing's position statement on nursing research states that "nursing research encompasses a wide scope of scientific inquiry including clinical research…clinical research based on biology, behavioral and other types of scientific investigation provide the scientific basis for care of the individual in any setting where nursing care is provided".[1]

On and off the battlefield, highly specialized, well-educated nurses are managing complex injuries as integral member of the trauma team. Decisions about what type, dose and route of medication to administer are within the scope of nursing practice for these nurses. Advanced nurses and all health care professionals involved in the care of the wounded warrior have a critical need for relevant data relative to optimize delivery of medications. Data generated in this study provides evidenced-based data for practitioners to use IO administration of atropine in the treatment of nerve agent casualties. There is a growing body of literature that supports the incorporation of IO administration of atropine in policies for the preparation and treatment of nerve agent poisoning. [2,3]

The aims of this study were to determine the pharmacokinetics of atropine when administered via the IO, IV, and IM routes in a hypovolemic swine model and determine the impact of hypovolemia on the rate and extent of absorption when administered via these routes. This study demonstrated that hypovolemia had a dramatic effect on the absorption of atropine delivered by intramuscular auto-injection. Conversely, hypovolemia had less effect on IV and IO delivery. We hypothesized that peripheral vasoconstriction caused by hypovolemia might delay uptake from IO administration and create an absorption phase in its pharmacokinetic profile. We did not see any evidence of this in our study. Our results indicate that therapeutic levels of atropine may be delayed and possibly difficult to obtain via IM injection in the presence of hypovolemic shock.

This study emphasizes the potential difficulty of treating nerve agent poisoning solely with IM atropine and the feasibility of treating nerve agent casualties with IO administration of atropine. This route of administration may be particularly advantageous when the casualty has had a severe exposure or is in hypovolemic shock.

Our findings are consistent with those of Murray and colleagues, whose study on the bioavailability of nerve agent antidotes in minipigs demonstrated rapid and complete bioavailability of atropine after IO administration.[4] However, in the same study the manual IM injection of atropine resulted in a more rapid absorption (3.5 vs 6.6 minutes) and higher peak concentrations (33.6 vs 20 ng/ml) than we observed with the use of an auto-injector.[4] Auto-injection has previously been found to have more rapid absorption and higher peak plasma concentrations than traditional IM injection.[5] Perhaps these differences are related to the muscle used for injection and/or the type of swine used for the experiment. The quadriceps muscle of a 20 Kg Gottingen minipig may have greater blood flow than the gluteal muscle of a 70 kilogram Yorkshire cross. In humans the IM administration of a 2 mg dose of atropine into the anterolateral aspect of the upper leg with the MARK 1 auto-injector resulted in a mean peak plasma concentration of 12.9 ng/ml and a median time to peak concentration of 6.5 minutes.[6]

The results may not be generalizable to humans; however, pigs are very similar in anatomy and physiology and should approximate results with humans. In fact, the tibia of a 70-kilogram pig is shorter and may contain less marrow than a human of the same weight. This difference may underestimate any distribution or depot effect. Additionally, the results may be specific to tibial IO administration and not generalizable to sternal IO administration. The sternum has a smaller marrow volume and is made up of red marrow compared to the adult tibia which is made up of almost entirely yellow marrow. In theory, the sternal IO route should exhibit less distribution because of its lower fat content and marrow volume.

The findings of this study supports the incorporation of IO administration of atropine in policies for the preparation and treatment of nerve agent poisoning. Additional studies should be conducted with different IO sites of administration such as the sternum and humerus. Future research should also be conducted on the bio equivalency other common medications used in the treatment of nerve agent such as 2 PAM Cl and diazepam.

Changes in Clinical Practice, Leadership, Management, Education, Policy, and/or Military Doctrine that Resulted from Study or Project

None to date

References Cited

1. AACN Position Statement on Nursing Research http://www.aacn.nche.edu/publications/position/nursing-research (accessed 28 Sep 2016)

2. Yost J, Baldwin P, Bellenger S, Bradshaw F, Causapin E, Demotica R, Livingston M, Lee C, Gegel B, Burgert J, Claessens A, Johnson D, Loughren M, Pharmacokinetics of intraosseous atropine in hypovolemic swine. Am J Disaster Med. 2015. 10(3); 217-222
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Summary of Dissemination

Type of Dissemination	Citation	Date and Source of Approval for Public Release
Publications	Yost J, Baldwin P, Bellenger S, Bradshaw F, Causapin E, Demotica R, Livingston M, Lee C, Gegel B, Burgert J, Claessens A, Johnson D, Loughren M, Pharmacokinetics of intraosseous atropine in hypovolemic swine. Am J Disaster Med. 2015. 10(3); 217-222	Madigan Army Medical Center Public Affairs Office July, 2015
Publications in Press	none	
Published Abstracts	none	
Podium Presentations	Sarah Bellenger, Phillip Baldwin & Michael Loughren. Pharmacokinetics of IM, IV and IO Atropine in Normovolemic and Hypovolemic Swine. Biannual Phyllis J. Verhonick Meeting, San Antonio, Texas, May 2012 Sarah Bellenger, Cynthia Benton, Richelle Demotica, Michael Livingston, Jonathan Yost & Michael Loughren. Pharmacokinetics of IM, IV and IO Atropine in Normovolemic and Hypovolemic Swine. Washington Association of Nurse Anesthetists Spring Meeting, Seattle, Washington. April, 2011	Madigan Army Medical Center Public Affairs Office April, 2012 Madigan Army Medical Center Public Affairs Office April, 2011

Poster Presentations	Loughren, M., Demotica, R., Benton, C., Causapin, E., Yost, J., Burgert, J., Johnson, D. Pharmacokinetics of IM, IV and IO Atropine in Hypovolemic Swine, 17th Biennial Phyllis J. Verhonick Nursing Research Course, San Antonio, Texas, May 2012. Bellenger, S, Livingston, M, Baldwin, P, Bradshaw, F, Gegel, B, Johnson, D, Loughren, M, Pharmacokinetics of Intramuscular, Intravenous, and Intraosseous Atropine in Normovolemic Swine, AANA Annual Meeting in Boston, MA, August 2011. Demotica, R, Benton, C, Causapin, E, Yost, J, Burgert, J, Johnson, D, Loughren, M, Pharmacokinetics of Intramuscular, Intravenous, and Intraosseous Atropine in Hypovolemic Swine, AANA Annual Meeting in Boston, MA, August 2011.	Madigan Army Medical Center Public Affairs Office April, 2012 Madigan Army Medical Center Public Affairs Office July, 2011 Madigan Army Medical Center Public Affairs Office July, 2011
Media Reports	None	
Other		

Reportable Outcomes

Reportable Outcome	Detailed Description
Applied for Patent	None
Issued a Patent	None
Developed a cell line	None
Developed a tissue or serum repository	None
Developed a data registry	None

Recruitment and Retention Aspect	Number
Animals Projected in Grant Application	40
Animals Purchased	40
Model Development Animals	4
Research Animals	36
Animals With Complete Data	35
Animals with Incomplete Data	1

One pig in the hypovolemic IV administration group died in the final minutes of the experiment. The data from that pig were analyzed and modelled but the results were vastly different (greater than 3 standard deviations) from the rest of the group and therefore, excluded from statistical analysis.

Final Budget Report